Summary Report

Spironolactone

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946-06

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

October 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

Table of Tables

Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of spironolactone (UNII code: 27O7W4T232), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how spironolactone is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how spironolactone has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of spironolactone and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Spironolactone was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and Sincerus Florida, LLC. Spironolactone was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Spironolactone was nominated to treat an unspecified medical condition via various topical routes of administration (gel, cream, ointment, solution, suspension, etc) at a strength based on the prescriber's request; therapeutic dose ranges from 2-5%. The nominators state that spironolactone is generally used to treat acne and topical fungal infections.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of spironolactone.[6-14]

Reasons provided for nomination to the 503B Bulks List included:

- Compounded product may be the only product to effectively treat the indication for which it is intended
- Patient need for dosage form or strength, including greater concentration, that is not available commercially
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products
- Manufacturer backorder
- The use of a finished product can potentially introduce unacceptable inaccuracies into the compounded medication
- There are no topical spironolactone products to compound from and excipients from oral dosage forms would be undesirable in topical formulations

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of spironolactone products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language;

and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for spironolactone; name variations of spironolactone were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing spironolactone. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: spironolactone, and topical administration or form (refer to Appendix 1 for full search strategies). Results were limited to human studies in English language. Searches were conducted on February 16, 2021. In addition, the ECRI Guidelines Trust® repository was searched on February 16, 2021 for clinical practice guidelines that recommended the use of spironolactone and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which spironolactone was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if spironolactone was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or an unspecified dosage form or ROA. Studies in which spironolactone was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of spironolactone; setting; total number of patients; number of patients who received spironolactone; patient population; indication for use of spironolactone; dosage form and strength; dose; ROA; frequency and duration of therapy; use of spironolactone in a combination product; use and formulation of spironolactone in a compounded product; use of spironolactone compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances spironolactone was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use spironolactone. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of spironolactone in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Spironolactone is not available as an FDA-approved product in the nominated dosage form and ROA. Spironolactone is available as FDA-approved oral tablet and suspension products.
- Spironolactone is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for spironolactone.
- Spironolactone is not available in the nominated dosage form and ROA in any of the national medical registries reviewed.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 336 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 378 titles and abstracts were screened. After screening, the full text of 126 articles was reviewed. Finally, 8 studies were included. One hundred eighteen studies were excluded for the following reasons: wrong study design (98 studies); unspecified dosage form or ROA (9); non-nominated dosage form or ROA (6); unable to obtain full text (2); wrong substance (2); language other than English (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 8 included studies were published between 1986 and 2020. There were 8 experimental studies conducted in the following countries: Egypt, France, Iran, Italy, Switzerland, the UK, and the US.

A total of 327 patients participated in the 8 included studies. The number of patients in each study ranged from 12 to 78.

Outcome measures differed among the included studies and included: acne severity index, completion of intervention, development of rash, functional outcome, hair growth, histological thickness of epidermis, non-inflammatory lesions, patient satisfaction, sebum excretion rate, side effects, total acne lesions.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of spironolactone

One hundred twenty patients received topical spironolactone as a treatment for acne vulgaris, applied twice daily in concentrations ranging from 1-5% for 6 weeks to 2 months. Twelve patients received topical spironolactone as a treatment for androgen-dependent hirsutism applied daily in a concentration of 5% for 3 months. Forty patients received topical spironolactone as a treatment for androgenetic alopecia, applied twice daily as a concentration of 1% for 12 months. Eight patients received topical spironolactone as a treatment for epidermal growth factor receptor (EGFR) inhibitor-induced generalized rash, applied twice daily as a concentration of 5% for 4 weeks. Fifteen patients received topical spironolactone for scar prevention after top surgery, applied twice daily as a concentration of 5% for 12 months. Twenty-three patients received topical spironolactone as a treatment for skin atrophy associated with topical clobetasol use, applied daily as a concentration of 5% for 29 days.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Spironolactone was used as a compounded product and used in a combination product (refer to Tables 8-10).

In 1 study, the authors' concluding statement recommended the use of topical spironolactone for the treatment of skin atrophy associated with topical clobetasol use.[15] In 1 study, the authors concluded that the use of topical spironolactone was not recommended for the treatment of androgen-dependent hirsutism.[16] In 6 studies, the authors concluded that further studies were necessary for the use of topical spironolactone for the treatment of acne vulgaris, androgenetic alopecia, EGFR inhibitor-induced generalized rash, and scar prevention associated with top surgery.[6,10,17-20] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

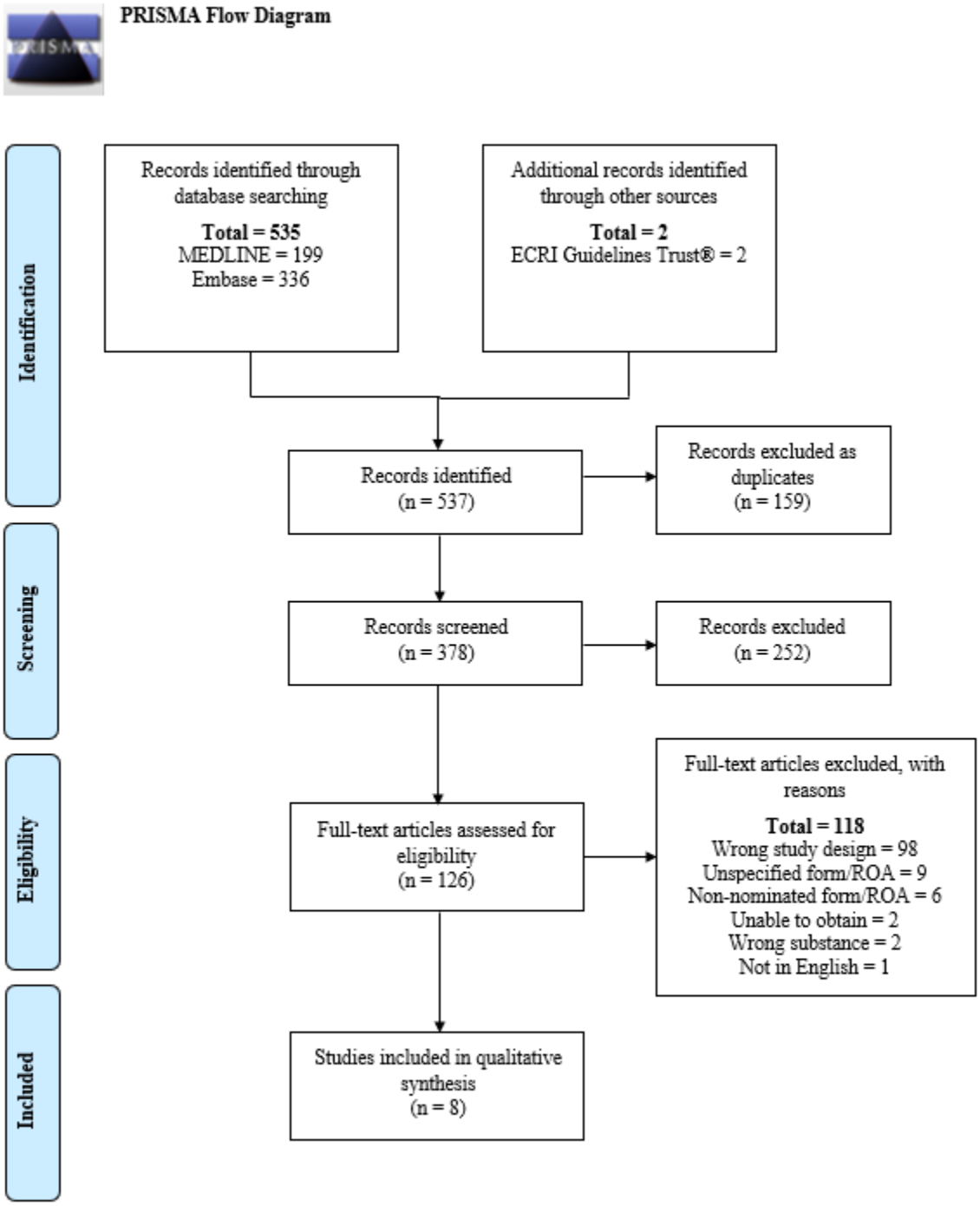
In addition to the 8 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of spironolactone.

As an aldosterone antagonist and a potassium sparing diuretic, spironolactone is widely used to treat patients with hypertension.[18] However, spironolactone is also a synthetic steroid that "acts as an anti-androgen by altering steroidogenesis and by affecting target organ response to circulating end organs."[6] As a result of its anti-androgenic properties, other indications for oral spironolactone include the treatment of acne, hirsutism, and androgenetic alopecia.[6,21]

Hirsutism – "the presence of excessive hair growth in women" – is often caused by increased androgen production and additionally is affected by increased androgen sensitivity in hair follicles and sebaceous glands.[22] The effect of androgen on sebaceous glands can lead to increased secretion of sebum and result in acne.[22] As a result, antiandrogens, such as combined oral contraceptive pills or spironolactone, have been used to treat these conditions in female patients.[23] While spironolactone may be used in male patients, it is associated with a side effect of feminization, and in some patients may cause gynecomastia.[23]

In 1 article from U.S. Pharmacist, a formula is provided for an acne gel containing spironolactone 4 g, niacinamide 4 g, and cimetidine 1 g.[24]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive	0
Observational	0
Experimental[6,10,15-20]	8

Table 4. Number of studies by country

Country	**Number of Studies**
Egypt[18]	1
France[15]	1
Iran[6,10]	2
Italy[20]	1
Switzerland[16]	1
UK[17]	1
US[19]	1
	Total US: 1 Total Non-US Countries: 7

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Acne					
Afzali *et al.*, 2012, Iran[6]	Double-blind clinical trial	78 Patients with mild or moderate acne • Spironolactone (21.1%, mean 21.5 y ± 4.2) • Placebo (15%, mean 22.2 y ± 4.06)	• Spironolactone (38) • Placebo (40)	Total acne lesions, acne severity index	"Therefore, more robust and long-term studies with varied doses of topical spironolactone appear necessary to confirm the probable roles played by spironolactone in the treatment of acne lesions."
Kelidari *et al.*, 2016, Iran[10]	Randomized, double-blind, prospective trial	60 Patients with mild to moderate acne vulgaris • Spironolactone loaded nanostructured lipid carrier (SP-NLC; 12.5%, mean 21.80 y ± 5.97) • Spironolactone alcoholic gels (SP-ALC; 6.67%, mean 20.86 y ± 5.36)	• Spironolactone loaded nanostructured lipid carrier (30) • Spironolactone alcoholic gels (30)	Mean number of total lesions, non-inflammatory lesions	"The therapy of [spironolactone loaded nanostructured lipid carrier] and [spironolactone alcoholic gels] were well tolerated and resulted in significantly greater improvement in mild to moderate acne vulgaris after 8 weeks treatment in comparison to the baseline."
Walton *et al.*, 1986, UK[17]	–	31 Patients with moderately severe facial acne (53.3%, age not specified)	• Spironolactone powder dispersed in Unguentum Merck (11) • Spironolactone cream (11) • Potassium canrenoate and lactic acid cream (9)	Sebum excretion rate	"These observations suggest that topical spironolactone is unlikely to be beneficial in treating acne."
Indication 2: Androgen-dependent hirsutism					
Gomez *et al.*, 1987, Switzerland[16]	Placebo-controlled double-blinded study	12 Patients with moderate androgen-dependent hirsutism (0%, age not specified)	• Spironolactone (12) • Placebo (12) All patients received both treatments on different skin areas	Hair growth	"Hirsutism and hair growth were not influenced by the application of the spironolactone-containing cream, either during the first month of treatment or during the subsequent 2 months following removal of hair."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Androgenetic alopecia					
Abdel-Raouf *et al.*, 2020, Egypt[18]	Randomized and comparative study	60 Patients with androgenetic alopecia (58%, mean 30.96 y ± 7.3)	• Minoxidil (20) • Spironolactone (20) • Spironolactone and minoxidil (20)	Increase in anagen hair	"In conclusion, spironolactone prepared as 1% topical gel and minoxidil prepared in a concentration of 5% could be applied safely in twice daily dose that could be effective in the treatment of [androgenetic alopecia] in both sexes. In addition, their combination in one topical dosage form may increase the efficacy and would achieve better advantages."
Indication 4: Epidermal growth factor receptor inhibitor-induced generalized rash					
Le-Rademacher *et al.*, 2019, US[19]	Double-blind, placebo-controlled trial	17 Patients scheduled to begin treatment with panitumumab or cetuximab (76.4%, range 39-82 y)	• Spironolactone (8) • Placebo (9)	Development of non-facial rash, development of rash where spironolactone was not applied	"Epidermal growth factor receptor inhibitor-induced rash appears to be androgen-mediated; antiandrogen therapy merits further study for rash prevention/palliation."
Indication 5: Scar prevention associated with top surgery					
Tanini *et al.*, 2020, Italy[20]	Prospective randomized controlled study	30 Patients who underwent transition through double incision mastectomy with nipple and areola grafts (100%, range 20-23)	• Top Surgery Scar go containing spironolactone, alfa bisabolol, and silicone gel (15) • Standard silicone gel (15)	Functional outcome, side effects, satisfaction	"Although further studies and an increased group number are necessary to better assess the efficacy and validity of [Top Surgery Scar go], our product seemed to be a very promising new alternative treatment for scar management after top surgery in transmen."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 6: Skin atrophy					
Maubec *et al.*, 2015, France[15]	Randomized, double-blind, crossover phase 2 efficacy trial	23 Volunteers receiving topical clobetasol (26.1%, range 21.1-49.6 y)	• Clobetasol (23) • Spironolactone (23) • Spironolactone and clobetasol (23) • Placebo (23)	Histological thickness of the epidermis	"These findings identify [mineralocorticoid] as a factor regulating epidermal homeostasis and suggest that topical [mineralocorticoid] blockade could limit glucocorticoid-induced epidermal atrophy."

Abbreviation: "–", not mentioned.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Epidermal growth factor receptor inhibitor-induced generalized rash[19]	Apply twice daily	5%	–	Topical	4 weeks

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Acne vulgaris[6,10,17]	Apply twice daily	1-5%	Cream, Gel	Topical	6 weeks – 2 months
	Apply 1 g twice daily				
Androgen-dependent hirsutism[16]	Apply 30-60 mg daily	5%	Cream	Topical	3 months

Androgenetic alopecia[18]	Apply twice daily	1%	Gel	Topical	12 months
Scar prevention associated with top surgery[20]	Apply twice daily	5%	Galenic preparation	Topical	12 months
Skin atrophy[15]	Apply daily	5%	Gel	Topical	29 days

Table 8. Number of studies by combination

	Combination Formula	**Number of Studies**
Nominated	Spironolactone 2% / Benzoyl peroxide 2.5-5% / Clindamycin 1% / Niacinamide 2-4% / Tretinoin 0.025-0.05% – topical	0
	Spironolactone 2% / Clindamycin 1% / Hydrocortisone 0.5% / Niacinamide 2% / Tretinoin 0.025% – topical	0
	Spironolactone 2% / Benzoyl peroxide 5% / Clindamycin 1% / Niacinamide 2% – topical	0
	Spironolactone 2% / Clindamycin 1% / Niacinamide 4% / Tretinoin 0.025% – topical	0
	Spironolactone 2% / Clindamycin 1% / Niacinamide 2% – topical	0
	Spironolactone 5% / Dapsone 6-8.5% / Niacinamide 2% – topical	0
	Spironolactone 5% / Niacinamide 2% / Tretinoin 0.025-0.05% – topical	0
	Spironolactone 5% / Ketoconazole 2% – topical	0
	Spironolactone 5% / Niacinamide 4% – topical	0
Others found in literature	Spironolactone 5% / Alfa bisabolol 5% – topical galenic preparation[20]	1
	Spironolactone 5% / Clobetasol 0.05% – topical gel[15]	1
	Spironolactone 1% / Minoxidil 5% – topical gel[18]	1

Table 9. Compounded products – US

No compounded products from included studies

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Acne vulgaris[10]	• Solid stearic acid (2.8 g) was combined with liquid oleic acid (1.2 g), lipophilic surfactant Span 80 (2.5 g) and spironolactone (1 g) and melted using hot plate • Hot lipid was dispersed in a 1/3 (28.77 g) of aqueous solution of hydrophilic surfactant Tween 80 to form a coarse pre-emulsion through sonication • Mixture was dispersed into remaining 2/3 of hydrophilic surfactant solution, maintained in ice bath • Dispersion was incorporated into 1% Carbopol gel with preservative methyl paraben (0.2 g) and allowed to hydrate for 24 hours • Resulting mixture was stirred and neutralized with tri-ethanolamine to obtain semisolid Carbopol gel matrix	Gel	1%
	• Spironolactone (5 g) was dissolved in hydroxyethyl cellulose (5 g) and propylene glycol (10 g) under stirring • Water (78.8 g) was added to solution with continuous stirring, followed by addition of methyl paraben (0.2 g) and Carbopol (1 g) • Final solution neutralized by triethanolamine to obtain the final gel		5%
Androgenetic alopecia[18]	• Gelling agent hydroxyl propyl methyl cellulose sodium salt was dispersed in distilled water and heated with continuous stirring • Dispersion was allowed to cool to room temperature • Drugs in specified concentrations were dissolved or levigated in ethyl alcohol and added dropwise to gel with continuous stirring	Gel	1%

Results of interviews

One hundred eighty-four SMEs were contacted for interviews; 64 agreed to be interviewed, and 120 declined or failed to respond to the interview request. One SME discussed spironolactone; this SME was a medical doctor who specialized and/or was board-certified in dermatology, working in an academic medical institution for 1 year. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

While the SME was unfamiliar with the use for fungal infections, they said that spironolactone is helpful for hormonal acne. It is normally administered orally and is used chronically rather than as an in-office application.

The SME thought that oral spironolactone would be more convenient and more effective when compared to topical ROA; "because if you're trying to treat hormonal changes that are including acne, you probably want a systemic dose." But at the same time, they do not know "for sure" that topical application is not effective and noted that it would potentially be safer regarding side effects associated with systemic spironolactone, such as hyperkalemia.

Spironolactone is specifically used for hormonal acne, which usually happens "in women and on the jawline and can happen in middle age as well as in adolescence." It is not used for the "more run of the mill, adolescent acne." However, the SME also commented that "a lot of acne is multi-factorial;" as a result, sometimes they use combinations of medications with differing mechanisms of action to treat the acne. But they usually use commercially available products to treat acne, and a fair amount are available OTC; "I probably would tell them to get the separate medications, particularly if they're over-the-counter, because they're probably going to be cheaper than having something compounded. And so, that's another factor that probably should be taken into account." If the patient comes in with mild acne, they would probably start with either a topical retinoid or a benzoyl peroxide wash. For patients with more moderate acne, they will be using multiple products and starting to consider systemic agents, depending upon the patient's lifestyle, how bothered they are by the acne, and their timeline for needing a resolution (if they need a quick resolution versus having a few months to treat). For patients needing a quick resolution, they would be started on an oral antibiotic; if there are stubborn cysts, they might receive some steroid injections. They would also add a retinoid for a long-term benefit.

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient products contained within the spironolactone nomination.

Spironolactone 5% / niacinamide 4% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. None of the active ingredients contained within this product are available as an FDA approved drug intended for topical administration. Spironolactone is added for its antiandrogen properties and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Spironolactone 5% / niacinamide 2% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients butylated hydroxytoluene, butylparaben, ethanol, methylparaben, mineral oil, titanium dioxide, and trolamine, which are components of the commercially

available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Spironolactone is added for its antiandrogen properties, niacinamide for its skin conditioning benefits, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Spironolactone 5% / niacinamide 2% / tretinoin 0.05% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients butylated hydroxytoluene, butylparaben, ethanol, methylparaben, mineral oil, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Spironolactone is added for its antiandrogen properties, niacinamide for its skin conditioning benefits, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Spironolactone 5% / dapsone 6% / niacinamide 2% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without methylparaben as an inactive ingredient, which is a component of the commercially available products. This inactive ingredient is known to be a harmful allergen or irritant; its hazardous concerns include human endocrine disruptor and human immune and respiratory toxicant or allergen. Spironolactone is added for its antiandrogen properties, dapsone for its anti-inflammatory properties, and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Spironolactone 5% / dapsone 8.5% / niacinamide 2% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without methylparaben as an inactive ingredient, which is a component of the commercially available products. This inactive ingredient is known to be a harmful allergen or irritant; its hazardous concerns include human endocrine disruptor and human immune and respiratory toxicant or allergen. Spironolactone is added for its antiandrogen properties, dapsone for its anti-inflammatory properties, and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Spironolactone 2% / clindamycin phosphate 1% / niacinamide 4% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is

used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, and propylene glycol which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as a skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, violation of industry recommendations, restricted in cosmetics; use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin. Spironolactone is added for its antiandrogen properties, clindamycin for its antibacterial properties, niacinamide for its skin conditioning benefits, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Spironolactone 2% / benzoyl peroxide 5% / clindamycin phosphate 1% / niacinamide 2% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients, butylated hydroxytoluene, butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen possible human carcinogen, violation of industry recommendations, restricted in cosmetics; use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin. Spironolactone is added for its antiandrogen properties, benzoyl peroxide for its ability to remove oil from the skin, clindamycin for its antibacterial properties, niacinamide for its skin conditioning benefits, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Spironolactone 2% / benzoyl peroxide 5% / clindamycin phosphate 1% / niacinamide 2% / tretinoin 0.05% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients, butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, possible human carcinogen, violation of industry recommendations, restricted in cosmetics; use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin. Spironolactone is added for its antiandrogen properties, benzoyl peroxide for its ability to remove oil from the skin, clindamycin for its antibacterial properties, niacinamide for its skin conditioning benefits, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA approved drug products and because this

combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event, refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants, refer to Tables 15-18 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtain varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated "we have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from one outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use-dates compared to products compounded in-house allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a STAT medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a five-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor and another commented that "we absolutely buy as many presser drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant, while they do not obtain a lot of products from outsourcing facilities, stated that "when we do purchase from 503B's, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also impacted the operations of hospitals with one participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making with one participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready to use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established clean room and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use-date that can be assigned to these products and, as the participant stated, "we obviously need to provide product with much extensive beyond use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with mid-size hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "we might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law."

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used with one-hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers stating that "predatory pricing on premixes is present in the market."

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be

possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately, even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said "I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration a 503B isn't going to go through the expense of adding that to their product list." The participant continued that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big it won't fit,' we want it in this format and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose, is it a unit dose or isn't it."

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that "most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end" and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage" continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that "what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Hospital Pharmacists] and the FDA allows." This "adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages."

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, "I think the FDA has really looked closely at API, and they're slowly pushing the 503B outsourcers to a sterile to sterile." Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative containing product. So, there is a need for this product to be compounded from API as a preservative free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded for bulk... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative free is also an issue for ophthalmic products, however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate clean room with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, "However, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products with one stating "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated "there's not many 503Bs are doing the non-sterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded

alum in-house from non-sterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up but, when I asked about their process for verifying the sterility, as you would with a sterile product, we do USP [United States Pharmacopeia] <71> Sterility Testing. They couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "when you need it, it's an emergency" and another noting that it "is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it STAT shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, 'this is an old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into "a very specific kind of pump that's used to deliver a very specific kind of chemotherapy." When there are breaks in the chemotherapy regimen, the pump has to be filled with something and by using glycerin "it can go three months or something like that, so it's a huge patient satisfier to have that concentration available." The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis with one commenting that "our nephrologists, like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs." There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use-date is limited to 12-24 hours depending on storage which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility they also compound a proprietary formulation in house. This participant observed that "it is complicated to do in-house. We do it on a, Baxa 1200 or 2,400, either one, compounder. Then we send it up to for pH and potassium testing.

Obviously, then we're confined to 797 beyond-use-dates versus longer beyond-use-dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to the "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that "Traditionally, we've found 503B's to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503B's where we've had agreements for certain products to take it off our plate, and then low and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

Results of survey

The survey was not approved for distribution by any professional medical associations.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Amongst respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products

from outsourcing facilities. Refer to Table 17 for the categories of products obtained from outsourcing facilities.

Spironolactone was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

Survey not distributed by any professional medical associations

Table 12. Conditions for which spironolactone prescribed or administered

Survey not distributed by any professional medical associations

Table 13. Reasons for using compounded spironolactone

Survey not distributed by any professional medical associations

Table 14. Use of non-patient-specific compounded spironolactone

Survey not distributed by any professional medical associations

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N=102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2

Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N=38)**
< 50	4
50-99	3
100-199	1
200-299	3
300-399	5
400-599	3
> 600	18

[a]Respondents allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N=143)[a]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19

Other[b]	6

[a]Respondents allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

Categories	Responses, n (N=142)[a]
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[a]Respondents allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 18. Products obtained from an outsourcing facility

Product	Responses, n (N=108)[a]
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0

Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0

Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Spironolactone was nominated for inclusion on the 503B Bulks List as various single and multi-ingredient topical formulations for an unspecified medical condition. Spironolactone is not available in the nominated dosage form and ROA in any of the medical registries searched.

From the literature review, topical spironolactone is used for a variety of indications such as acne, hirsutism, alopecia, EGFR inhibitor-induced generalized rash, scar prevention associated with top surgery, and skin atrophy. There were 2 included literature review studies that used compounded topical spironolactone gel for acne and alopecia.

From the interview conducted, the SME said that spironolactone is helpful for hormonal acne. The SME thought that oral spironolactone would be more convenient and more effective when compared to topical ROA; “because if you’re trying to treat hormonal changes that are including acne, you probably want a systemic dose.” The SME noted that topical spironolactone would potentially be safer regarding side effects associated with systemic spironolactone, such as hyperkalemia. Because acne can be multi-factorial, sometimes combinations of medications with differing mechanisms of action to treat the acne. There is a fair amount of OTC commercially available acne products, which would be probably cheaper than compounding a medication.

From the Phase 3 project, 1 nominator provided additional information regarding the multi-ingredient products contained within the spironolactone nomination. Spironolactone will be compounded as a topical gel in combination with additional API as a multi-ingredient product to treat acne. Spironolactone is added for its antiandrogen properties.

The survey was not approved for distribution by any professional medical associations.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Afzali BM, Yaghoobi E, Yaghoobi R, Bagherani N, Dabbagh MA. Comparison of the efficacy of 5% topical spironolactone gel and placebo in the treatment of mild and moderate acne vulgaris: a randomized controlled trial. *J Dermatolog Treat.* 2012;23(1):21-25.
7. Bagherani N. Efficacy of topical spironolactone in treatment of acne. *Dermatol Ther.* 2015;28(3):176.
8. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol.* 1985;112(1):124-125.
9. Charny JW, Choi JK, James WD. Spironolactone for the treatment of acne in women, a retrospective study of 110 patients. *Int J Womens Dermatol.* 2017;3(2):111-115.
10. Kelidari HR, Saeedi M, Hajheydari Z, et al. Spironolactone loaded nanostructured lipid carrier gel for effective treatment of mild and moderate acne vulgaris: A randomized, double-blind, prospective trial. *Colloids Surf B Biointerfaces.* 2016;146:47-53.
11. Layton AM. Top ten list of clinical pearls in the treatment of acne vulgaris. *Dermatol Clin.* 2016;34(2):147-157.
12. Lessner E, Fisher S, Kobraei K, et al. Spironolactone and topical retinoids in adult female cyclical acne. *J Drugs Dermatol.* 2014;13(2):126-129.
13. Rathnayake D, Sinclair R. Use of spironolactone in dermatology. *Skinmed.* 2010;8(6):328-332; quiz 333.
14. Shaw JC, White LE. Long-term safety of spironolactone in acne: results of an 8-year followup study. *J Cutan Med Surg.* 2002;6(6):541-545.
15. Maubec E, Laouenan C, Deschamps L, et al. Topical mineralocorticoid receptor blockade limits glucocorticoid-induced epidermal atrophy in human skin. *Journal of Investigative Dermatology.* 2015;135(7):1781-1789.
16. Gomez F, Ramelet AA, Ruedi B, Muhlemann M. Lack of effect of a spironolactone-containing cream on hair growth in hirsute women. *Dermatologica.* 1987;174(2):102-103.
17. Walton S, Cunliffe WJ, Lookingbill P, Keczkes K. Lack of effect of topical spironolactone on sebum excretion. *British Journal of Dermatology.* 1986;114(2):261-264.

18. Abdel-Raouf H, Aly UF, Medhat W, Ahmed SS, Abdel-Aziz RTA. A novel topical combination of minoxidil and spironolactone for androgenetic alopecia: Clinical, histopathological, and physicochemical study. *Dermatologic Therapy.* 2020:e14678.

19. Le-Rademacher JG, Rowland K, Atherton PJ, et al. Androgen mediation-and antiandrogens mitigation-of the epidermal growth factor receptor (egfr) inhibitor-induced rash: Results from a pilot randomized trial and small translational case series. *American Journal of Hospice & Palliative Medicine.* 2019;36(6):519-525.

20. Tanini S, Calabrese S, Fisher AD, Maggi M, Lo Russo G. When testosterone needs to be contrasted: A preliminary study of scar prevention in transmen top surgery with an innovative galenic preparation. *Aesthetic Plastic Surgery.* 2020;44(3):1006-1013.

21. Treating female pattern hair loss. *Harvard Women's Health Watch.* 2009;16(10):1-3.

22. Brown J, Farquhar C, Lee O, Toomath R, Jepson RG. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database Syst Rev.* 2009(2):Cd000194.

23. Cooper AJ, Harris VR. Modern management of acne. *Med J Aust.* 2017;206(1):41-45.

24. Allen Jr LV. Spironolactone, niacinamide, and cimetidine acne gel. *US Pharmacist.* 2012;37(12):43-44.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to February 15, 2021
- Date last searched: February 16, 2021
- Limits: Humans (search hedge); English language
- Number of results: 199

1	spironolactone/	6823
2	espironola#ton$.tw.	6
3	spironola#ton$.tw.	6013
4	spirothiobarb$.tw.	1
5	or/1-4	9200
6	administration, topical/	38889
7	administration, cutaneous/	22495
8	skin absorption/	11855
9	topical$.tw.	108892
10	transcutaneous$.tw.	14884
11	epicutaneous$.tw.	2047
12	transdermal$.tw.	15053
13	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11638
14	exp gels/	53703
15	emulsions/	18535
16	suspensions/	7853
17	liniments/	124
18	ointments/	12869
19	skin cream/	1105
20	pharmaceutical solutions/	3318

21	gel?.tw.	312791
22	emulsion?.tw.	34471
23	suspension?.tw.	111680
24	liniment?.tw.	148
25	ointment?.tw.	12175
26	salve?.tw.	345
27	paste?.tw.	12971
28	unguent$.tw.	114
29	lotion?.tw.	2387
30	cream?.tw.	19567
31	shampoo?.tw.	1451
32	solution?.tw.	724460
33	or/6-32	1349468
34	and/5,33	320
35	exp animals/ not humans/	4788182
36	34 not 35	221
37	limit 36 to english language	199

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 16, 2021
- Limits: Humans (search hedge); English language
- Number of results: 336

1	‘spironolactone'/mj	9577
2	‘espironolacton*':ti,ab,tn	24
3	‘espironolakton*':ti,ab,tn	0
4	‘espironolatton*':ti,ab,tn	0
5	‘spironolacton*':ti,ab,tn	9812
6	‘spironolakton*':ti,ab,tn	9
7	‘spironolatton*':ti,ab,tn	1
8	‘spirothiobarb*':ti,ab,tn	2
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	15091
10	‘topical drug administration'/de	84320
11	‘cutaneous drug administration'/de	751
12	‘transdermal drug administration'/de	9302
13	‘skin absorption'/de	8172
14	‘topical treatment'/de	13830
15	‘topical*':ti,ab	154117
16	‘epicutaneous*':ti,ab	3470
17	‘transdermal*':ti,ab	21965
18	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18390
19	‘cream'/de	9827
20	‘gel'/exp	81180
21	‘liniment'/de	257
22	‘lotion'/de	2967

23	‘ointment'/de	18278
24	‘paste'/de	2552
25	‘salve'/de	170
26	‘suspension'/de	28626
27	‘emulsion'/exp	47896
28	‘shampoo'/de	2344
29	‘cream$':ti,ab	30575
30	‘emulsion$':ti,ab	46585
31	‘liniment$':ti,ab	242
32	‘lotion$':ti,ab	4116
33	‘ointment$':ti,ab	22006
34	‘paste$':ti,ab	15480
35	‘salve$':ti,ab	485
36	‘unguent*':ti,ab	242
37	‘gel$':ti,ab	367775
38	‘suspension$':ti,ab	148427
39	‘shampoo$':ti,ab	2271
40	‘solution$':ti,ab	896121
41	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	1718772
42	#9 AND #41	538
43	[animals]/lim NOT [humans]/lim	6169563
44	#42 NOT #43	409
45	#42 NOT #43 AND [english]/lim	336

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)
    - ○ Betamethasone acetate
    - ○ Betamethasone dipropionate
    - ○ Betamethasone sodium phosphate
    - ○ Cholestyramine resin
    - ○ Cimetidine
    - ○ Clobetasol propionate
    - ○ Clotrimazole
    - ○ Cromolyn sodium
    - ○ Dexamethasone sodium phosphate
    - ○ Diclofenac sodium
    - ○ Finasteride
    - ○ Fluconazole
    - ○ Fluticasone propionate
    - ○ Hydrocortisone
    - ○ Itraconazole
    - ○ Ketoconazole
    - ○ Lidocaine hydrochloride
    - ○ Methylprednisolone acetate
    - ○ Metronidazole
    - ○ Mupirocin
    - ○ Niacinamide
    - ○ Phytonadione (vitamin K1)
    - ○ Prilocaine
    - ○ Spironolactone
    - ○ Sulfacetamide sodium monohydrate
    - ○ Terbinafine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Zinc oxide

- None of the above

3. Do you prescribe the compounded topical products that you selected in in combination with other active pharmaceutical ingredients as a multi-ingredient product?
    - Yes
    - No
    - I'm not sure
4. Why do you use the compounded topical products that you selected? (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing these products
    - Other (please explain) _____
5. Do you stock non-patient-specific compounded products at your practice?
    - Yes
    - No
    - I'm not sure
6. I obtain compounded products from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
7. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
8. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify specialtiy(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilites.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

- Fluids
- Ophthalmic preparations
- Patient-controlled analgesia
- Ready-to-use anesthesia syringes
- Ready-to-use antibiotic syringes and/or bags
- Ready-to-use electrolyte solutions
- Ready-to-use vasopressor solutions
- Total parenteral nutrition solutions
- Other, please identify _____

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - Calcium chloride
    - Caffeine sodium benzoate
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Anesthesiology	Society of Cardiovascular Anesthesiologists	Declined – failed to respond
Cardiology	American Academy of Cardiovascular Perfusion	Declined
	American Board of Cardiovascular Perfusion	Declined – failed to respond
	American Society of Extracorporeal Technology	Declined – failed to respond
Dermatology	American Academy of Dermatology	Declined – failed to respond
Naturopathy	American Association of Naturopathic Physicians	Agreed
Nephrology	American Society of Diagnostic and Interventional Nephrology	Declined
Ophthalmology	American Academy of Ophthalmology	Declined – failed to respond
	American Society of Cataract and Refractive Surgery	Agreed
	American Society of Retina Specialists	Declined
Podiatry	American Podiatric Medical Association	Agreed
Psychiatry	The International Society for Electroconvulsive Therapy and Neurostimulation	Agreed
Rheumatology	American College of Rheumatology	Agreed
Surgery	American Association of Neurological Surgeons	Declined – failed to respond
	American Association for Thoracic Surgery	Declined – failed to respond
	American College of Surgeons	Declined – failed to respond
	American Society for Reconstructive Microsurgery	Declined – failed to respond
Urology	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction	Declined
Wound Care	Association for the Advancement of Wound Care	Declined – failed to respond

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.